Exhibit B

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
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M E M O R A N D U M

Date: June 10, 2009

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Cc: Julie Beitz, M.D., Office Director, ODE 3, CDER
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Re: DDDP Consult# 1157

The Office of Compliance is working on a possible injunction for a company selling black salve to cure skin cancer, among other things. These types of black salve products have been known to be corrosive to the skin, at times disfiguring people. OC is seeking DDDP opinion on the potential hazard of using these products topically.

Material Reviewed:

Labels for Aldara and Efudex

Adhami V et al, Activation of Prodeath Bcl-2 Family Proteins and Mitochondrial Apoptosis Pathway by Sanguinarine in Immortalized Human HaCaT Keratinocytes. *Clin Cancer Res.* 2003 Aug 1; 9(8):3176-82.

Adhami V et al Sanguinarine causes Cell Cycle Blockade and Apoptosis of Human Prostate Carcinoma Cells via Modulation of Cyclin Kinase Inhibitor-Cyclin-Cyclin-dependent kinase machinery. *Mol Cancer Ther* 2004; 3:933-40.

Affleck AG, et al, A Case of Do-It-Your-Self Mohs's Surgery Using Bloodroot Obtained from the *Internet. Sr J Dermatol.* 2007 Nov; 157 (5): 1 078-9.

Ahmad N, et al, Differential Antiproliferative and Apoptotic Response of Sanguinarine for Cancer Cells Versus Normal Cells. *Clin Cancer Res* 2000; 6: 1524.

Brooks NA., Fixed-Tissue Micrographic Surgery in the Treatment of Cutaneous Melanoma. An Overlooked Cancer Treatment strategy. *J Dermatol Surg Oncol.* 1992 Nov; 18(11): 999-1000.

Brown CW Jr, et al. Auto-Mohs.com *Dermatol Surg.* 2001 Nov; 27(11):975-8.

Cassens B. Warning letter to Best on Earth Products, May 20, 2008.

Jellinek N, Maloney ME., Escharotic and Other Botanical Agents for the Treatment of Skin Cancer: a Review. *JAm Acad Dermatol.* 2005 Sep;53(3):487-95.

Kalish RS, et al, Experimental rationale for Treatment of High-Risk Human Melanoma with Zinc Chloride Fixative Paste. Increased Resistance to Tumor Challenge in Murine Melanoma Model. *Dermatol Surg.* 1998 Sep; 24(9):1021-5.

Karayilanoglu T et al. The Protective and Therapeutic Effects of Zinc Chloride and Desferrioxamine on Skin Exposed to Nitrogen Mustard. *Mil Med* 2003; 168: 614-7.

In the matter of Lois March, M.D. Before the Georgia Office of State Administrative Hearings. Filed July 26, 2005.

Laub DR Jr., Death from Metastatiç Basal Cell Carçinoma: Herbal Remedy or Just Unlucky? *J Plast Reconstr Aesthet Surg.* 2008 Jul; 61 (7):846-8.

Moran AM, Helm KF, Histopathologic Findings and Diagnostic Difficulties Posed With Use of Escharotic Agents for Treatment of Skin Lesions: a Case Report and Review of the Literature. *J Cutan Pathol.* 2008 Apr; 35(4):404-6.

McDaniel S, Goldman GD., Consequences of Using Escharotic Agents as Primary Treatment for Nonmelanoma Skin Cancer. *Arch Dermatol.* 2002 Dec 138(12):1593-6.

Osswald SS et al, Self- Treatment of a Basal Cell Carcinoma with "Black and Yellow Salve". *JAm Acad Dermatol.* 2005 Sep; 53(3): 523-5.

Rodriguez-Fragoso L et al, Risks and Benefits of Commonly Used Herbal Medicines in Mexico. *Toxicol Appl Pharmacol.* 2008 Feb 15; 227(1): 125-35.

Saltzberg F et al, Deforming Self-Treatment with Herbal "Black Salve, *Dermatol Surg* 2009; 35:1–3.

Schaffer J et al, Cutaneous Melanoma—Past, Present, and Future. *JAm Acad Dermatol*. 2004 July 51 (1): 65-9.

Tromovitch T, Stegman S. Microscopic-Controlled Excision of Cutaneous Cancers. *Cancer*. 1978; 41:653-658.

Background:

"Black Salve" is a colloquial term for a number of different compounds containing escharotic agents as their primary active ingredients. Escharotic agents are caustic, corrosive substances that produce a thick coagulated crust (an eschar) and subsequently a scar. Examples of escharotic agents include zinc chloride, bloodroot and goldenseal.[1] These preparations often are combined with additional herbal ingredients including Galangal Root, Ginger Root, Graviola, Bitter Melon Seed, Nordihydroguaiaretic Acid, Neem Oil, Plantain, Chapparal leaves, and Sheep Sorrel.

Zinc chloride

Zinc chloride is perhaps the best known of these products. Historically, it had been used in the early 19th century as a treatment for skin cancer. More recently it has been used for the chemical debridement of leg ulcers[2] and to debride osteomyelitic bone[3]. There is evidence in the dermatologic literature of some biologic activity beyond that of a destructive agent for zinc chloride. In 1998 Kalish et al demonstrated increased resistance to tumor challenge in a murine melanoma model that had been treated with zinc chloride paste as a fixative prior to excision.[4] In 2003 Karayilanoglu demonstrated that zinc chloride may prevent nuclear damage to the skin of guinea pigs after exposure to nitrogen mustard.[5]

Zinc chloride was introduced to the conventional medical community in 1930 by Fredrick Mohs who used it as a tissue "fixative" in the preliminary stages of the "micrographic technique" he pioneered as a treatment for skin cancer.[6] It is important to note that Mohs never used the technique of "chemodestruction" alone but always as a preliminary to surgical excision with margin evaluation by histopathologic sectioning of the specimen.

Zinc chloride has a slow onset of action, requiring 24 hours of contact for fixation. The advantage it provided of a bloodless field for surgery was eventually offset by its disadvantages- unpredictable penetration, lack of selectivity of the destruction (i.e. normal tissue was also destroyed). In 1978 Tromovitch and Stegman introduced the concept of "fresh frozen tissue sampling" to replace chemical fixation in the Mohs procedure, citing the decreased pain, shorter surgical times, lack of destruction of normal tissue and the ability to do immediate repair as obvious advantages.[7] This has been widely accepted in the dermatological surgery community and "fresh frozen tissue sampling" has replaced chemical fixation as the standard of care in Mohs micrographic surgery.

Bloodroot

Bloodroot, also known as "pucoon, indian paint, redroot and snake bite" which contains the alkaloid sanguinarine, is derived from the root of Sanguinaria canadendid and other poppy fumaria species and can be found in the eastern US and Canada. [6] Bloodroot was included in the original formula used by Dr. Mohs as an organic stabilizer. In addition to its activity as an escharotic, bloodroot has been found to have antimicrobial, anti-inflammatory and anti-oxidant properties.

Specifically, in 2000 N. Ahmad reported that Sanguinaria canadensis has been shown in studies to induce selective apoptosis in cancer cells through inhibition of transcription factor nuclear factor-kB activation, inhibition of kappa B-alpha phosphorylation and degradation[8] Data from another study by Adhami and Ahmad in 2003 had shown the involvement of the mitochondrial pathway and Bcl-2 family of proteins during apoptosis of immortalized keratoinocytes.[9] In addition, a report of sanguinarine causing cell cycle blockade and apoptosis of prostate carcinoma cells through cyclin kinase inhibitor-cyclin-cyclin-dependent kinase machinery modulation has been shown by these same authors in 2004.[10]

Review:

There appears to be a "growing trend whereby patients self-treat skin cancers (basal cell, squamous cell, and melanoma) with unregulated, often internet acquired escharotic agents"[1]. Websites selling these "black salve" products are making unsubstantiated claims of cures, guaranteeing success in removal of malignant lesions, and offering testimonials and anecdotal reports as support for these claims. These websites often stress the "natural" aspect of their products (knowing that patients often associate "natural" with "safe"), citing long history of use in "native" cultures and in some cases vilifying "conventional evidenced-based western medicine"[6].

The escharotic agents often contain zinc chloride and bloodroot as primary components in varying concentrations. The strength and purity of these products are unknown. There is a lack of scientifically documented proof of efficacy and no proof of tissue selectivity. These products are being offered for treatment of both nonmelanoma and melanoma skin cancer which are conditions that are not amenable to self-diagnosis. Under these circumstances it is not possible to provide adequate directions so that a layman can use the products safely".[2]

Some of the websites touting the use of escharotic agents as treatments for skin cancer, presumably as a means of legitimatizing their claims, have referenced Dr. Fredrick Mohs, failing to mention that surgery was always an integral part of his approach. In fact, in 1948 Dr. Mohs denounced the practice of use of escharotics without surgery as a treatment for skin cancer citing that it caused "excessive mutilation" and was an "unreliable cure".[6]

Case reports are appearing in the dermatologic literature with increasing frequency citing cases of incomplete removal of tumor with subsequent scarring masking recurrence thus requiring more

invasive definitive procedures because of the delay in diagnosis and appropriate therapy.[1, 6] In 2007 Laub reported a death from metastatic basal cell carcinoma as a result of the "false cure from treatment with topical escharotic therapy".[11]

The use of these products can also result in marked scarring requiring numerous subsequent surgeries in an attempt to achieve an acceptable cosmetic outcome.[12] There are examples in the literature of extensive mutilation with complete loss of nasal ala[13] and exposed bone at the shoulder[14]. There is no control of the extent of the destruction of surrounding normal tissue with these nonselective agents.

Since these patients are often self-treating without benefit of a histologic diagnosis (biopsy) some of these cases of extensive scarring may be the result of treating benign lesions. The even more worrisome instance, with regard to long term outcome for the patient, is the self-treatment of melanoma.

Ironically, this is taking place at a time when conventional medicine has an extraordinary proven track record of successful treatment of skin cancer. Cure rates of 99% for primary basal cell, 94% for recurrent basal cell, 97% for primary squamous cell and 90% for recurrent basal cell are achieved with Mohs micrographic surgery.[12, 15] For those patients who refuse surgery (out of fear, concern about cosmetic outcome or inability to tolerate surgery), there are topical products with proven safety and efficacy against at least certain subsets of non-melanoma skin cancer which are FDA-approved. These include Aldara and Efudex.

According to the label approved in 2007, Aldara is indicated for the topical treatment of "biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured." Composite clinical cure (visual and histologic) at 12 weeks averaged 75% in the original pivotal studies. In a separate 5 year open label study which is still ongoing, clinical cures (without histology) were 90% at 12 weeks and were maintained at the 2 year follow-up point in 79% of patients treated.

According to the label from 2005, Efudex in the 5% strength is "also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites". The success rate is approximately 93% based on 113 lesions in 54 patients.

With regard to melanoma, the most important prognostic indicator is the depth of penetration of the lesion measured in millimeters into the skin, which is known as the Breslow level. Use of any treatment without prior biopsy or excision to determine this important factor would be absolutely contraindicated. Depth of penetration is felt by most experts to be, in at least some cases, related to the length of time the lesion has been present. Early detection and prompt surgical treatment is the only measure known to improve the prognosis of melanoma. Cure rates for melanoma have improved over time as the depth of the lesion at the time of diagnosis has lessened. In the 1950's when the mean Breslow depth was >3mm the 5 year survival rate was 50%. This improved to

80% in the 1970's when mean Breslow was 2 mm and again in the 1990's to 90% with a mean Breslow ≤ 1mm.[16] Overall 5 year survival rates for in-situ (no penetration of the dermis) melanoma averages 100%.

The prognosis worsens with deeper penetration as shown below:

	Clark's Level	5 year survival (average)
Level I	intraepidermal (in situ)	100%
level II	penetrates the papillary dermis;	95%
level III	spans the papillary dermis	82%
level IV	penetrates the reticular dermis;	71%
Level V	penetrates into the subcutaneous fat.	49%

With a disease such as melanoma, any treatment without proven efficacy, particularly one often employed without histologic diagnosis, can cause a delay in diagnosis with life-threatening consequences.

In conclusion, against a backdrop of excellent cure rates with conventional surgical treatment for both melanoma and nonmelanoma skin cancer there is no place for the use of an unproven product such as "Black salve". In addition to delay in diagnosis and therefore potentially decreasing cure rates and increasing morbidity these unpredictable topicals can cause extensive and nonselective destruction and unnecessary scarring.

References

1. Jellinek N, Maloney ME., Escharotic and Other Botanical Agents for the Treatment of Skin Cancer: a Review. *JAm Acad Dermatol.* 2005 Sep; 53(3):487-95.

2. Cassens B. Warning letter to Best on Earth Products, May 20, 2008.

3. Osswald SS et al, Self- Treatment of a Basal Cell Carcinoma with "Black and Yellow Salve". *JAm Acad Dermatol.* 2005 Sep; 53(3): 523-5.

4. Kalish RS, et al, Experimental rationale for Treatment of High-Risk Human Melanoma with Zinc Chloride Fixative Paste. Increased Resistance to Tumor Challenge in Murine Melanoma Model. *Dermatol Surg.* 1998 Sep; 24(9):1021-5.

5. Karayilanoglu T et al. The Protective and Therapeutic Effects of Zinc Chloride and Desferrioxamine on Skin Exposed to Nitrogen Mustard. *Mil Med* 2003; 168: 614-7.

6. McDaniel S, Goldman GD., Consequences of Using Escharotic Agents as Primary Treatment for Nonmelanoma Skin Cancer. *Arch Dermatol*. 2002 Dec 138(12):1593-6.

7. Tromovitch T, Stegman S. Microscopic-Controlled Excision of Cutaneous Cancers. *Cancer*. 1978; 41:653-658.

8. Ahmad N, et al, Differential Antiproliferative and Apoptotic Response of Sanguinarine for Cancer Cells Versus Normal Cells. *Clin Cancer Res* 2000; 6: 1524.

9. Adhami V et al, Activation of Prodeath Bcl-2 Family Proteins and Mitochondrial Apoptosis Pathway by Sanguinarine in Immortalized Human HaCaT Keratinocytes. *Clin Cancer Res.* 2003 Aug 1; 9(8):3176-82.

10. Adhami V et al Sanguinarine causes Cell Cycle Blockade and Apoptosis of Human Prostate Carcinoma Cells via Modulation of Cyclin Kinase Inhibitor-Cyclin-Cyclin-dependent kinase machinery. *Mol Cancer Ther* 2004; 3:933-40.

11. Laub DR Jr., Death from Metastatiç Basal Cell Carçinoma: Herbal Remedy or Just Unlucky? *J Plast Reconstr Aesthet Surg*. 2008 Jul; 61 (7):846-8.

12. Brown CW Jr, et al. Auto-Mohs.com *Dermatol Surg*. 2001 Nov; 27(11):975-8.

13. Saltzberg F et al, Deforming Self-Treatment with Herbal "Black Salve, *Dermatol Surg* 2009; 35:1–3.

14. In the matter of Lois March, M.D. Before the Georgia Office of State Administrative Hearings. Filed July 26, 2005.

15. Moran AM, Helm KF, Histopathologic Findings and Diagnostic Difficulties Posed With Use of Escharotic Agents for Treatment of Skin Lesions: a Case Report and Review of the Literature. *J Cutan Pathol*. 2008 Apr; 35(4):404-6.

16. Schaffer J et al, Cutaneous Melanoma—Past, Present, and Future. *JAm Acad Dermatol*. 2004 July 51 (1): 65-9.